REMARKS

Status of Claims

Claims 1-34, 43-45, 51, and 55 stand rejected as allegedly obvious under 35 U.S.C. § 103(a) by U.S. Patent No. 6,251,407 to Ganne ("Ganne") in view of the Barnett et al. article reproduced in Vaccine, Vol. 16, No. 7, pp. 746-754 (1998) ("Barnett article" or "Barnett") and U.S. Patent Application No. 2002/0058040 to Grimes et al. ("Grimes").

Reply to Claim Rejections Under 35 U.S.C. § 103(a)

35 U.S.C. § 103(a) states:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-34, 43-45, 51, and 55 stand rejected as allegedly obvious under 35 U.S.C. § 103(a) by U.S. Patent No. 6,251,407 to Ganne ("Ganne") in view of Barnett, and U.S. Patent Application No. 2002/0058040 to Grimes et al. ("Grimes"). The Patent Office misapprehends the present claims, the cited references, and Applicants' previous arguments. Applicants respectfully submit that there would have been no reason for one of ordinary skill in the art to have combined the teachings of Ganne with those of the secondary references. Secondly, even if one of ordinary skill in the art were to combine the references in the manner suggested by the Patent Office, a composition as claimed would not result. Finally, even if properly rejected as *prima facie* obvious, Applicants respectfully continue to urge that the invention nonetheless patentably defines over the applied prior art by virtue of the unexpected results obtained by Applicants.

The present invention relates to a composition comprising:

at least one frozen antigenic medium; and

at least one frozen adjuvant;

wherein the composition is in a solid state,

and wherein the at least one frozen antigenic medium and the at least one frozen adjuvant each comprise one or more phases which are distinct from each other; and

wherein the composition would be in the liquid state at a temperature greater than or equal to 4°C.

The present invention is aimed at developing vaccines which can be stored for several years and which are ready for use after thawing.

The Cited References Do Not Disclose a Motivation to Store the Composition in Frozen Layers

As noted in the Response dated November 21, 2007 to the Office Action mailed May 31, 2007, which is incorporated herein by reference, the primary reference Ganne discloses an emulsion (see col., 3, ll. 45-54), or compositions created by "simple mixing" (see col. 10, ll. 3-6). Ganne does not disclose storage for the composition created, except to state that the composition "must be stable preferably for at least 12 months when it is stored at 4°C." Ganne, col. 3, ll. 59-61. Ganne does not disclose long term storage of the composition, or that the composition of the at least one antigenic medium and the at least one adjuvant may have longer storage capabilities when the composition elements are stored separately. Separation of the antigenic medium and the adjuvant into phases in a solid state is not disclosed or suggested in Ganne. As Ganne does not disclose or suggest freezing compositions at all, it necessarily cannot disclose or suggest separate phases in a solid state.

Moreover, neither Barnett nor Grimes discloses or suggests storing compositions in frozen layers. Barnett, as described below, only discloses that concentrated, inactivated antigen "at ultralow temperatures" may be stockpiled to later use to make vaccine. There is no indication that the compositions are in a frozen state and, depending on the solvent systems employed, it will be appreciated that even at

ultralow temperatures, certain solvents will not freeze. Grimes, as described below, only discloses a frozen *emulsified* composition.

Thus, looking at the references collectively, there is simply not provided any reason, teaching, suggestion or motivation for one of ordinary skill in the art to provide a composition as claimed including discreet frozen antigen and adjuvant. Indeed, the teachings of Grimes would appear to point in the precise opposite direction as Grimes discloses freezing of an emulsified composition which, by design, is one that is not separated into discrete phases.

The Combination of Ganne, Barnett, and Grimes Does Not Disclose All Elements of the Claims

The secondary references fail to remedy the deficiencies of Ganne. Grimes discloses a method for stable frozen storage of emulsified immunogenic compositions. Grimes, Abstract. Grimes discloses:

> Although freezing the emulsion was originally employed as a gentle method to separate the conjugate-bearing aqueous phase from the emulsion for easier sampling and analysis, the emulsions preparations according to this invention surprisingly did not break down even when expired to several freeze-thaw cycles. This stability under the repeated freeze/thaw stress was all the more surprising because frozen storage of emulsions had not been previously considered an option. Freezing and thawing was generally held to be detrimental to the stability of emulsions, perhaps leading to disruption of conjugates and aggregation or separation of emulsion components.

Grimes, paragraph [0043]. The composition described in Grimes, when emulsified, frozen, and thawed, was still found to exhibit activity. See Grimes, paragraph [0048] and Examples 1 and 2. Throughout the specification, however, the composition is emulsified *before* it is frozen. See Examples 1 and 2, paragraphs [0053] ("[i]n accordance with the present protocol, emulsions were prepared by mixing 410 ml in the Silverson

500 ml mixing head, at 8,000 rpm for 4 minutes. . .") and [0070] ("[t]he mixture was prepared and emulsified under aseptic conditions. . .").

It is clear that if one of ordinary skill in the art were to combine the teachings of Ganne with Grimes, a product as claimed would not result. The application of the teachings of Grimes, which, as described, teaches a frozen emulsification, to the therapeutic composition of Ganne would result in an frozen *emulsification* of the therapeutic composition. Such a combination would not disclose at least "at least one frozen antigenic medium; and at least one frozen adjuvant. . ." as disclosed in claim 1, and "freezing at least one antigenic medium into a solid state, . . . and freezing the at least one adjuvant into a solid state. . ." as disclosed in claim 55. Indeed, quite to the contrary, the whole point of emulsification is to maintain components in a blended state, which would direct one of ordinary skill in the art away from providing discrete phases as is claimed.

The Barnett article does not overcome the deficiencies enunciated above with respect to Ganne and Grimes. As discussed in the May 21, 2008 response, the Barnett article discloses an examination of "[t]he protective ability of two novel oil-based FMD vaccines in pigs." Barnett, abstract. The compound(s) used in Barnett are markedly distinct from the compounds disclosed in the present application. The Examiner relies on Barnett for the proposition that "concentrated stocks of vital antigen are stable for years when frozen. . . ." February 21, 2008 Office Action, page 2. Barnett discloses that, to create an "emergency ring-vaccination," "many FMD-free states have access to FMD vaccine banks, which primarily store concentrated, inactivated FMDV antigens at ultralow temperatures." Barnett, p. 746, col. 2. The antigens may be used to create vaccines; the vaccines themselves are not stored in the FMD vaccine bank. Barnett does not disclose or suggest the desirability to freeze a solid state composition, where the "one or more phases [] are distinct from each other." Barnett only discloses that antigen at an ultralow temperature may be stockpiled to later use to make vaccine, which may or may not be frozen.

In contrast, independent claims 1 and 55 disclose a "solid state" composition, where the "one or more phases [] are distinct from each other." Neither Ganne, Grimes, nor Barnett, alone or in combination, discloses a frozen, solid state composition, where the "one or more phases [] are distinct from each other." Ganne does not suggest that it is desirable to freeze the composition, Grimes does not disclose or suggest a frozen layered composition, and Barnett discloses only freezing an antigen, to later thaw and make vaccine. There is no suggestion, explicitly or implicitly, of the desirability of having separate solid antigenic medium and adjuvant phases in a single composition wherein the composition would be in a liquid state at temperature greater than or equal to 4°C, as recited in the present claims. As none of the cited references, alone or in combination, suggests the desirability of their combination, explicitly or implicitly, there is no motivation to combine the references. The combination of references is improper and should be withdrawn.

Moreover, even when combined, the teachings of the cited references are deficient. The combination of the teachings would not result in the claimed multi-phase composition wherein at least one antigenic medium and the at least one adjuvant each comprise one or more phases which are distinct from each other and wherein the composition would be in the liquid state at a temperature is greater than or equal to 4°C, as recited in the claims. Ganne, for example, does not disclose that the composition of the at least one antigenic medium and the at least one adjuvant may have long term storage problems. Grimes only discloses that an emulsified composition may exhibit activity after frozen storage, but the composition, in all cases in Grimes, is emulsified *before* it is frozen and stored. Although the tendency to resort to "hindsight" in examining an application is often difficult to avoid, impermissible hindsight must be avoided and the legal conclusion must be based on facts gleaned from the prior art. MPEP § 2142. Applicants respectfully submit that independent claims 1 and 55 are therefore allowable.

Finally, even if it were *prima facie* obvious to combine the applied prior art in the manner suggested by the Patent Office, Applicants note that the claimed composition is

non-obvious by virtue of the unexpected results observed by Applicants. For example, as set forth at page 20 of the originally filed application, a vaccine prepared in phases remained active after being stored at -20°C for seven months, while vaccines prepared as an emulsion and stored at the same temperature and for the same duration lost their activity. Pages 21 to 25 of the application also outline trials of the vaccines prepared in phases and vaccines in an emulsion. The trials show that the vaccines prepared in phases "is more effective than a vaccine composition containing the same constituents but which was stored for the same period and at the same temperature in the form of an emulsion (froze) of the various phases." *See* p. 24. The longer stability at frozen temperatures is an unexpected result of the phase preparation as taught in claims 1 and 55. Grimes does not disclose the long term stability of a layered composition, instead only disclosing that a frozen *emulsification* may have longer term storage possibilities. Grimes does not disclose or suggest that a frozen layered composition may exhibit long term storage possibilities. The Patent Office has failed to provide any evidence that separation of the antigen and adjuvant phases as claimed would result in a more stable composition.

Claims 2-34, 43-45, and 51 depend from independent claim 1, and Applicants submit that they are themselves allowable at least because of their dependence from allowable independent claim 1. Applicants therefore respectfully request that the rejection of claims 1-34, 43-45, 51, and 55 under 35 U.S.C. § 103(a) be withdrawn.

A New Form of a Known Compound May Be Nonobvious

In the Response document dated February 5, 2009, Applicants cited *In re Berry* for the proposition that a new form of a compound may be nonobvious. In response, the Office Action notes that "the court decided it was not obvious because of the different between crystal and amorphous which is not the case here because the compounds are the same and the difference of freezing is not a different structure in that the frozen antigen is still antigen and the frozen adjuvant is still adjuvant." Office Action, page 3. Applicants respectfully disagree. Applicants respectfully submit that

the unexpected results obtained by the storage of the composition in phases is an unexpected property of the composition that is different from the properties of the emulsified composition of Ganne. Applicants also respectfully submit that the products in *In re Berry* had similar chemical composition (crystalline aluminum oxide), but were produced in different forms.

CONCLUSION

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

The Commissioner is hereby authorized to treat any current or future reply, requiring a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. In the event of any variance between the amount enclosed and the fees determined by the U.S. Patent and Trademark Office, please charge or credit any such variance to the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,

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Dated: Sept 25, 2009 By: _____

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